Remarks

Reconsideration of this Application is respectfully requested.

Claims 2-11 and 13-34 are pending in the application. Based on the following remarks, Applicant respectfully requests that the Examiner reconsider the outstanding rejection and that it be withdrawn.

Record of Telephonic Interview.

Applicant received an "Interview Summary" from the July 18, 2001 telephone conference with the Examiner. On the "Summary" form the box indicating it was *not* necessary for Applicant to provide a separate record of the interview was *not* checked. Therefore, for the record, Applicant indicates that during the telephone discussion, the issue discussed concerned whether all claims had been properly considered in view of Applicant's "Supplemental Amendment of January 16, 2001. Based on the discussion it was determined that in the Final Office Action considered claims 23-34 filed in the Supplemental Amendment of January 16, 2001.

Rejection Under 35 U.S.C. § 103.

In the Office Action mailed March 27, 2001 at page 2, the Examiner rejected claims 2-11, 13-22 and newly added 23-34 under 35 U.S.C. § 103 as allegedly being unpatentable over Sambrook et al. (Molecular Cloning: A Laboratory Manual, Second Edition; Cold

Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989 - hereinafter "Sambrook") in combination with Chomczynski (5,346,994) (hereinafter "Chomczynski") and Perlman (U.S. Patent No. 5,098,603) (hereinafter "Pearlman"). Applicant respectfully traverses this rejection, incorporates by reference herein and reiterates and expands upon the Amendment and Reply Under 37 C.F.R. § 1.111 filed November 8, 2000.

The Examiner's comments on the Rejection and Applicant's analysis.

The Examiner summarized the claims as follows:

> Claims 2 - 11 are directed to an RNA isolation reagent comprising at least one nonionic detergent (0. 1 - 1.0%), a chelating agent (20 - 250 mM), a phenol (10%-60%),and a phenol stabilizer (15-55%).
>
> Claims 13-34 are directed to a RNA extraction reagent and a method for providing cytoplasmic RNA from a sample comprising miking [sic] said sample with an RNA extraction reagent comprising at least one nonionic detergent, at least one phenol and at least one phenol solubilizer, adding a haloalkane to the mixture and precipitating cytoplasmic RNA.

Contrary to the Examiner's summary of the claims, not all of claims 23-34 are drawn to a "reagent" requiring "phenol solubilizer." Similarly, not all the "methods" of claims 13-20 require a phenol solubilizer in the RNA extraction reagent.

Based on the current summary of the claims and the lack of sufficient explanation in the rejection, it is unclear which aspects of the rejection specifically apply to the "RNA extraction reagent" and which aspects of the rejection apply to the "method for providing cytoplasmic RNA from a sample." The Office Action has failed to make this clear. To properly reject a method claim, each and every step of the method as a whole must be found in the art. Therefore, the Examiner must consider the claims to the "reagent" and those claims to the "method" individually. If the Examiner maintains any aspect of the rejection,

he is respectfully requested to more explicitly explain the manner in which the rejection applies to either the reagent or the method of using the same.

For the record, Applicant wishes to suggest a more appropriate way to consider the claims than has been done in the current Office Action. This should facilitate consideration of this reply and more expeditious prosecution. The claims should be considered in the following manner:

1) Claims 2-11 and 21-34 are drawn to a) an aqueous RNA extraction reagent comprising at least one nonionic detergent, at least one phenol and at least one phenol solubilizer in a range of given concentrations or b) an RNA extraction reagent comprising at least one nonionic detergent, at least one phenol and at least one chelator in a range of given concentrations. More specifically, claims 21 and 25-33 require a phenol solubilizer, while claims 6, 8, 9 and 22 require a chelator. The remaining claims of this product group are drawn to further modifications of one or both of the claimed reagents.

2) Claims 13-20 are drawn to a method for providing RNA from a sample, said method comprising *inter alia*, mixing the sample with an RNA extraction reagent from the claims of group 1 and of extracting RNA adding a haloalkane to the mixture.

The above manner of considering the claims, addresses at least in-part, some of the issues raised in the Office Action and Applicant's reply thereto. Applicant respectfully suggests that the Examiner is rejecting claims to a "reagent" (composition) based on a perceived interpretation of art describing "methods" of isolating or purifying nucleic acids (e.g. *see* Sambrook - E.3). Nowhere in the cited art, either singly or in combination, is there sufficient disclosure to render obvious either the claimed RNA extraction reagent or a method of using the same. Merely citing individual steps of several different "methods"

that use individual components of the claimed reagent, is not sufficient to render obvious the claimed reagent or the method of using the same.

Prior to addressing the specifics of the rejection, Applicant provides the following general comments in order to place the reply in the appropriate context

The Examiner has failed to consider the individual limitations of the dependent claims separately from the independent claims.

The Examiner has broadly addressed the rejection to only the independent claims and provided no argumentation whatsoever to support a position that the dependent claims (other than perhaps 23 and 29) with their additional limitations are unpatentable. Therefore, the Examiner is respectfully requested to provide appropriate art or argumentation to support the obviousness rejection as it may be applied to the dependent claims of the invention. In the absence of such support, the dependent claims should be indicated to be allowable.

The Examiner has failed to consider the invention as a whole.

When making an obviousness rejection, the Examiner must consider the invention as a whole. A comparison must be made between the cited art as a whole and the claimed subject matter as a whole (*In re Langer and Haynes,* 465 F.2d 896 (C.C.P.A. 1972); *Datascope Corp. v. SMEC, Inc.,* 776 F.2d 320 (Fed. Cir. 1985)). This has not been done. The Examiner has failed to consider the invention as a whole because he has not provided any evidence from the art that the complete "RNA extraction reagent" or that the complete method of using the same reagent as claimed by Applicant was suggested in the art. Rather, the Examiner has merely pointed to individual elements of the invention in several different and distinct pieces of cited art.

In this regard, it appears that the Examiner is using the cited art to provide specific individual components of the RNA extraction reagent, out of context of the invention or the art as a whole. The Examiner has made arguments that are analogous to saying that merely because all the individual chemicals necessary (e.g. A, B, C and D) to make the reagent are present in the cited art, it would be obvious to make the combination of A+B+C+D in the concentration recited in the claims.

The Examiner has reconstructed the claimed invention only by picking and choosing disparate components from the cited art using knowledge obtained from the specification (which otherwise would not have been available). The Federal Circuit has stated that:

> [i]t is impermissible, however, simply to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from the references to fill the gaps . . . The references themselves must provide some teaching whereby the applicant's combination would have been obvious.

In re Gorman, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991).

More recently in *Ecolochem Inc. v. Southern California Edison*, 56 USPQ2d 1065, 1072 (Fed. Cir. 2000), the court reiterated this position stating that: "We cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." (Citations omitted). Applicant respectfully suggests that the Examiner has used *a priori* knowledge of the invention (i.e., the template) obtained from the specification and has taken isolated elements of Sambrook, Chomczynski and Perlman to attempt to fit them into the template, thereby approaching the claimed invention. For at least this reason, the rejection is incorrect and should be withdrawn.

Specifics of the rejection.

Specifically, in the Office Action beginning at the bottom of page 2, the Examiner addressed Applicant's arguments from the Reply filed November 8, 2000. The Examiner stated:

> Applicant asserts "that contrary to the Examiner's assertion, the specification at page 2 does not acknowledge that Sambrook discloses a method for isolating RNA that uses phenol." Although the instant specification does not state the use of phenol by Sambrook *et al.*, the use of a non-ionic detergent, RNAse inhibitors and no chaotropic agent by Sambrook *et al.* is cited, p.2, line 13, of the instant specification, wherein it is stated *"Sambrook (supra, at sections 7.6-7.9) discloses an alternative protocol for the isolation of cytoplasmic RNA extraction RNA from mammalian cells, which uses a nondisruptive RNA extraction reagent at physiological pH and salt concentration, instead of high concentrations of chaotropic salts. The extraction reagent contains an RNase inhibitor to protect the RNA during the isolation procedure and a nonionic detergent that solubilizes the cell membrane while leaving the nuclear membrane intact, to release cytoplasmic RNA."* Thus the use of a nonionic detergent within the art of nucleic acid purification is not novel within the art of RNA extraction. Along with the use of the nonionic detergent, the use of phenol and a solubilizer is not novel as Sambrook et al. teaches the use of phenol a haloalkane-chloroform and a solubilizer-isoamyl alcohol in the extraction of RNA (Appendix E.3 and B.5).

(Emphasis in original).

It is respectfully noted, that the Examiner agrees with Applicant's argument in the previous reply that the specification did "not acknowledge that Sambrook [where cited at sections 7.6-7.9] discloses a method for isolating RNA that uses phenol." Applicant, however, disagrees that Sambrook teaches "the use of phenol a haloalkane-chloroform and a solubilizer-isoamyl alcohol in the ***extraction of RNA*** (Appendix E.3 and B.5)" to obtain cytoplasmic RNA from a sample comprising cells. (Emphasis added).

Rather, in Appendices E.3 and B.5 Sambrook refers to the use of a phenol:chloroform:isoamyl alcohol mixture for removing "proteins from nucleic acid

solutions"(E3) or to "remove proteins from preparations of nucleic acids" (B5). Removing proteins "from nucleic acid *solutions"* or "preparation of nucleic acids" is not the same as "mixing said sample containing said cells with an RNA extraction reagent" as recited in for example, claim 13. Neither is the mixture for "removal of proteins" the same as an "RNA extraction reagent" as claimed for example in claims 21 or 22. The method of Sambrook at E.3 relates to chemical extraction of nucleic acid solutions. Therefore, the separate use of multiple reagents fails to render obvious Applicant's claimed multi-component reagent. Sambrook's teachings are also distinct from using a single multiple-component RNA extraction reagent[1] in the methods claimed by the Applicant.

Applicant also notes that the Examiner stated that "the use of the nonionic detergent, the use of phenol and a solubilizer is not novel." It is irrelevant to the patentability of the current claims whether the use of a "nonionic detergent" by itself is novel. It is also irrelevant whether the individual use of a phenol or a phenol solubilizer is novel. The issue is whether the complete "reagent" comprising all the recited components, i.e. the invention as a whole, as set forth in the pending claims, is not obvious. Applicant's reagents and methods of using the same are neither suggested nor taught by the combination of the applied art. Further, Applicant's invention is not directed to the use of single individual components in isolation. Rather one aspect of Applicant's claimed invention is a single

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[1]Applicant wishes to make clear that reference to "use of a single multi-component reagent" does not preclude the use of an additional reagent(s) such as e.g. a haloalkane in the claimed method, e.g. *see* claim 13(b). Rather, reference to a "single multi-component reagent" is used to indicate that one aspect of the invention involves a single reagent to be comprised of the components set forth in one or more of the claims. This clearly is distinct from the Examiner's attempt to arrive at the claimed invention by citing use of multiple reagents that may or may not together have all the components of the claimed "single-multi-component invention."

reagent comprised of multiple components as set forth in claims 21 and 22. Nowhere has the Examiner shown that such a single multi-component reagent or its use is obvious based on the applied art.

There is no motivation to combine Sambrook with Chomczynski.

At the end of the first paragraph of page 3, referring to Sambrook and Chomczynski, the Examiner stated that:

> Applicant seems to assert that one of skill in the art would not have a motivation to use a solubilizer with phenol based on the presence of other agents, even though the prior art teaches the use of phenol with a solubilizer in nucleic acid extractions wherein both chaotropic and non-chaotropic agents exist.

It is not clear how or why the Examiner arrived at this conclusion based on Applicant's previous argument in the Reply filed November 8, 2000. At page 5, third full paragraph, last 5 lines, the Applicant stated the following:

> One skilled in the art would not combine the Chomczynski solution for extracting RNA, DNA and proteins with the Sambrook *et al.* buffer for extracting RNA because, *inter alia,* the inclusion of a chaotropic agent, as taught by Chomczynski, in the Sambrook *et al.* buffer would cause co-isolation of polysaccharides so that the resulting RNA would not be in a purified form.

Applicant respectfully requests the Examiner to explain why one of skill in the art would have been motivated to combine Chomczynski and thereby make an RNA extraction buffer that co-isolates polysaccharides with the resulting RNA. In any event, even if Chomczynski is combined with Sambrook, the combination still fails to render obvious the claimed invention because the combination does not teach or suggest the invention as a whole.

At the bottom of page 3, the Examiner stated that:

> In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant application, applicant has not set forth reagents which have not been used in combination in the art for the extraction of RNA, moreover, the prior art has set forth the motivation for the use of the reagents cited supra in extraction reagents of RNA.

First, the Examiner is incorrect in asserting that the reagents of Applicant's claimed invention have previously been used in combination for extraction of "RNA." For example, as discussed above, Sambrook uses individual reagents to "remove proteins from nucleic acid *solutions*" not as RNA extraction reagents. Applicant respectfully suggests that the Examiner may be confusing a chemical extraction as described in the art with the extraction from cells as set forth in the claimed invention. For at least this reason, the rejection is incorrect and should be withdrawn.

Second, Applicant acknowledges the Examiner's citation of *McLaughlin*, however, as noted above by the Examiner, *McLaughlin* also cautions against using knowledge gleaned *only* from the Applicant's disclosure. This is exactly what the Examiner has done. Nothing in the cited art suggests Applicant's complete invention.

At the left hand column of *McLaughlin* at 212, the court stated that it "is not what the individual references themselves suggest but rather what the combination of disclosures taken as a *whole* would suggest to one of skill in the art." (Emphasis added). Nowhere has the Examiner shown that the alleged disclosures taken as a *whole* would suggest the claimed invention to one of skill in the art. Any one of innumerable combinations or concentrations of individual components could be contemplated based on the cited art. The Examiner has

failed to provide anything in the cited art that would suggest that one could obtain or use a single multi-component reagent of any sort whatsoever, to obtain RNA as is claimed in the present application. Applicant wishes to reiterate that nowhere in the applied art is the Applicant's invention suggested. For at least this reason the rejection is incorrect and should be withdrawn.

Third, in the paragraph cited above, the Examiner has made the statement that the "prior art has set forth the motivation for the use of the reagents cited supra . . ." Applicant respectfully requests the Examiner to specifically state what that motivation is and where it can be found in the art. In the absence of such support, the statement is merely conclusory and fails to support a proper rejection under 35 U.S.C. § 103. Nowhere has the Examiner shown that the combination of the applied art would render obvious the reagent of claims 21 or 22 which consists of multiple components.

The Federal Circuit has elaborated very clearly on the issue of combining known individual components in *Ecolochem* at 1073:

> Although the suggestion to combine references may flow from the nature of the problem, . . .'[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness, '. . . Therefore, '[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'

(Citations omitted).

Several of these errors have been made by the Examiner. The Examiner has defined the problem in terms of its solution. I.e. knowing that the solution to the problem is an "RNA extraction reagent," the Examiner has taken pieces from the art to obtain that solution. Assuming that the Examiner had not begun the rejection with the preconceived idea of the

invention, there is nothing in the art that would suggest the desirability and thus the obviousness of making the combination of components into a single extraction reagent as Applicant has done. Applicant respectfully requests that the Examiner provide from the prior art, that which suggests the desirability of making Applicant's combination of components. In the absence of such a suggestion the rejection cannot stand.

The cited art does not suggest the claimed combination of reagent components.

In the first full paragraph of page 4 of the Office Action, the Examiner next states that:

> Although the identical concentration ranges are not disclosed in the references cited supra, proportions of ingredients, to impart patentability to an otherwise obvious chemical composition, must produce more than a mere difference in degree in the properties of the composition. The proportions must be critical, i.e. they must produce a difference in kind rather than degree, which is not seen in the instant application.

Applicant does not believe that this is the correct basis for ignoring Applicant's argument concerning the different concentration ranges of components in the extraction reagent and respectfully requests the Examiner to provide a citation from either the MPEP or case law to provide the basis for the Examiner's argument. This position might be somewhat relevant if Applicant had merely made minor changes in concentrations of the components within a known reagent. However, nowhere has the Examiner shown that a single reagent of the such as one having the same components as Applicant's invention albeit at different concentrations already existed in the art.

Perlman's failure to suggest the concentration ranges of the invention fails to result in a prima facie case of obviousness based on the combination of the applied art.

In any event, as already pointed out, the difference in the concentration of EDTA in Perlman relative to that in the invention is *not* minor. Referring to Perlman at page 6, second full paragraph of the reply filed November 8, 2000 Applicant stated:

> Therefore, at best, the recitation pointed to by the Examiner teaches adding a *specific* concentration of EDTA, i.e. *0.1 to 10 mM* (preferably 1 mM) to a phenol solution, not an RNA isolation reagent. Contrary to this, claim 22 recites "at least one chelator at a concentration of 0.02-0.25 M" (i.e. 20 mM-250 mM) in a composition with additional components.

(Emphasis in original).

Thus, the higher end of Perlman's EDTA concentration range (10 mM) is only half of Applicant's lowest chelator concentration (0.02 M = 20 mM). Moreover, the suggested preferred EDTA concentration (i.e. 1 mM) in Perlman is only 5% of the lower end of Applicant's lower EDTA concentration range (20 mM) and less than 0.5% of the high end (0.25 M = 250 mM) of Applicant's concentration range. There is no reason whatsoever to assume that the concentration of at least the chelator in Applicant's extraction reagent of claim 22 would be obvious in view of Perlman. Moreover, the chelator is used for a different purpose than in the claimed invention and there is no suggestion to increase the chelator concentration to that used in the claimed invention.

Perlman suggests using a chelator to prevent oxidation of phenol.

In the Office Action at page 4, second full paragraph, the Examiner states:

> With regard to the use of chelators within the instant claims, claims 23 and 29 are drawn to the use of chelators with the instant composition. As cited in the office action mailed 5-9-2000, the motivation to use a chelator within the instant composition is clearly set forth in Perlman as "Perlman teaches (col. 4, lines 37-51) the use of chelators such as EDTA when

> performing nucleic acid extractions with phenolic solutions to remove traces of divalent metal ions, some of which are known to catalyze the oxidation of phenol; moreover, Perlman further teaches that when even minute traces of metal ions are present, phenol solution is prone to catalytic oxidation." , which counters applicant's assertion in the instant specification on p. 4, line 26 that the use of chelators to protect nucleic acids is novel. Given that 8-hydroxyquinoline has long been regarded in this art as a chelator of divalent cations, one of skill in the art would have a reasonable expectation of success in the use of 8-hydroxyquinoline with phenol to reduce catalytic oxidation per the teachings of Perlman.

Applicant respectfully disagrees.

Applicant respectfully suggests that the Examiner has overextrapolated from Perlman. Merely because Perlman may discuss the use of chelators to "prevent phenol oxidation," this does not suggest the desirability of including EDTA in the RNA extraction reagent of the claimed invention or that chelators would in any way protect nucleic acids. Further, Perlman is consistent with Applicant's assertion in the specification at page 4. The recitation beginning at line 25 of that page recites: "The present invention provides . . . the novel use of a chelator to protect the extracted RNA from degradation by Mg^{++} ions. . ." Nowhere has Perlman suggested that RNA would be protected by a chelator.

Additionally, the Examiner's assertion that based on Perlman, "one of skill in the art would have a reasonable expectation of success in the use of 8-hydroxyquinoline with phenol to reduce catalytic oxidation per the teachings of Perlman," is not pertinent to establishing a rejection under 35 U.S.C. § 103. The issue is not whether use of the cited art would result in a reasonable expectation of reducing catalytic oxidation, but whether there would be a reasonable expectation of obtaining the claimed invention when combining Perlman with the remaining cited art. A reasonable expectation of reducing catalytic oxidation is *not* a reasonable expectation of obtaining the claimed reagent or use of the same

based on the combination of art. Therefore this clearly results in a failure to provide a *prima facie* case of obviousness. For at least this reason the rejection should be withdrawn.

There is no motivation to combine DeBonnville with Sambrook or Chomcyznski and validity of the reagent claims is not in question.

At the last paragraph of page 4 the Examiner stated:

> Applicant's representative asserts that the DeBonville reference does not cure the deficiencies of Sambrook et al. or Chomczynski because "DeBonville *et al* is directed to methods of isolating DNA, not RNA. The DNA reagent composition contains, *inter alia*, phenol, isoamyl alcohol and 8-hydroxyquinoline. This composition does not contain the ingredients required to isolate RNA as set forth in the claimed reagents." If applicant's assertions are true, then the instant claims are also invalid with regard to the isolation of RNA given that these components are the same components applicant sets forth in claims 21 and 25, wherein phenol, a phenol solubilizer-exemplary of isoamyl alcohol, and 8-hydroxyquinoline are claimed.

In setting forth the rejection at the beginning of the Office Action the Examiner has not referred to DeBonville. Based on the above quoted paragraph, however, DeBonville still appears to be at issue and is therefore addressed by the Applicant. In this regard, Applicant respectfully submits that the Examiner may have misunderstood Applicant's argument. In the reply filed November 8, 2000, at the bottom of page 5, Applicant specifically argued:

> The third reference cited by the Examiner, DeBonville *et al.*, does not cure the deficiencies of Sambrook *et al.* or Chomczynski. DeBonville *et al.* is directed to methods of isolating DNA, *not* RNA. The DNA reagent composition contains, *inter alia*, phenol, isoamyl alcohol and 8-hydroxyquinoline. This composition does not contain the ingredients required to isolate RNA as set forth in the claimed reagents. Moreover, the reference is not analogous to the claimed invention or to the Sambrook *et al.* and Chomczynski references. One skilled in the art would not use a DNA isolation reagent to isolate RNA. As noted by DeBonville *et al.*, a preferred DNA isolation method employs RNase A which degrades RNA (see col. 3, lines 62-64). Clearly, one isolating RNA would not follow the DNA isolation methods outlined in the DeBonville *et al.* patent and would not combine such methods with any RNA isolation method.

(Emphasis in original).

Referring to the Examiner's statement that was cited at page 14 of this reply, Applicant respectfully suggests that the validity of the claims is not in question as the Examiner suggests. Rather, the issue is whether one of skill in the art would have had motivation to combine the cited art with DeBonville and if so would the combination teach or suggest the claimed invention. The answer is NO! This is particularly true since DeBonville is not analogous art. The Examiner still fails to provide any reason why one would combine a protocol for isolating DNA with one for isolating RNA in an attempt to obtain the claimed RNA extraction reagent or method of using the same. This is particularly true in view of the fact that DeBonville uses RNase which would destroy any RNA being extracted. Further, Applicant continues to maintain that DeBonville "does not contain the ingredients required to isolate RNA as *set forth in the claimed reagent*" because not only does it include RNase but it does not contain a nonionic detergent. For at least this reason the rejection is incorrect and should be withdrawn.

Summary.

Based on all of the above, there is no legal basis for the Examiner's approach to the § 103 rejection. Applicant has responded to the various arguments set forth by the Examiner as they appeared in the Office Action. Applicant now summarizes reasons why rejection is improper and the application is in condition for allowance.

The invention must be considered as a whole.

The Examiner has not considered the invention as a whole. The Court of Appeals for the Federal Circuit has clearly stated that:

> What we stressed in *Kimberly-Clark*, and have repeated many times since, was that 35 U.S.C. § 103 requires analysis of a claimed invention *as a whole*:. . . *What must be found obvious to defeat the patent is the claimed combination.*
>
> * * *
>
> Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.

The Gillette Co. v. S.C. Johnson & Son Inc. 16 USPQ2d 1923, 1927 (Fed Cir. 1990). (Emphasis in original).

Applicant contends that it is improper to concentrate simply on the fact that individual components of the RNA extraction reagent may or may not be cited in the applied art. In a footnote in *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 (Fed. Cir. 1986), the court described:

> . . . the following tenets of patent law that must be adhered to in applying § 102: (1) the claimed invention must be considered as a *whole*. . . (though the difference between claimed invention and prior art *may seem slight*, it may also have been the key to advancement of the art); (2) the reference must be considered as a whole and suggest the desirability and thus the obviousness of making the combination. . .

(Emphasis added).

In citing the secondary art the Examiner has only addressed individual elements of the invention (i.e. specific chemical compounds that become part of the completed reagent) and has failed to provide any evidence in the cited art or any art whatsoever that suggests the desirability of *combining* the compounds such that one of ordinary skill in the art would arrive at the limitations of the claims and thereby practice Applicant's invention.

The art cited by the Examiner provided no motivation to combine the teachings of the applied art to arrive at Applicant's invention.

In citing the secondary references, the Examiner has failed to provide any suggestion or motivation to combine the art. Nowhere has the Examiner indicated any basis for combining Sambrook, with Chomczynski, Perlman and DeBonville.

There is no expectation of successfully of obtaining the claimed invention based on the combination of the applied art.

As discussed above, the cited art fails to suggest many of the limitations of the claimed invention and therefore its combination would fail to successfully result in the claimed invention. Nowhere has the Examiner provided any evidence that the limitations of the dependent claims are found in the cited art or that such limitations would be suggested. Further, the use of RNAse as suggested by DeBonnville clearly would fail to result in a reagent for the extraction of RNA or the use of such a reagent. Merely because individual components of the invention may be used in an unrelated or unconnected context this fails to result in a reasonable expectation of obtaining the claimed invention.

The Examiner has failed to make a prima facie case of obviousness.

Applicants have addressed the specifics of this rejection above and will now summarize the reasons that the Examiner has failed to establish a *prima facie* case of obviousness. The MPEP at § 2143 sets forth three criteria that must be met in order to establish the *prima facie* case. These criteria are:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior

art reference (or references when combine) must teach or suggest all the claim limitations.

None of these criteria have been met.

First, the Examiner has failed to provide an appropriate motivation to combine the art cited in the rejection. The Examiner merely states at page 4, first paragraph of the Office Action that "the prior art has set forth the motivation for the use of the reagents cited supra in extraction reagents of RNA," however, the Examiner has failed to explain what that motivation actually is or where it is found in the applied art.

Second, the Examiner has failed to establish why there would be a reasonable expectation of successfully obtaining the claimed after combining the applied art. Nowhere has the Examiner provided why one would expect to successfully obtain the claimed invention following combination of the applied art.

Third, the Examiner has failed to establish that the combination of the applied art teaches or suggests all the claim limitations. For example, the use of Pearlman fails to remedy the very apparent deficit in terms of the appropriate concentration of chelator in the reagent of claim 22 and those claims dependent thereon. Further, nowhere has the Examiner shown that the combination of the applied art would result in a single reagent as in claims 21 or 22, the reagent claims dependent thereon having the specific limitations or the use of said reagents in a method for extracting RNA from a sample comprising cells. Thus, the Examiner has failed to provide a combination of art that teaches or suggest each and every limitation of the claimed reagents or their methods of use.

For all the reasons stated in this Reply, the Examiner has failed to establish a *prima facie* case of obviousness, the rejection is improper and should be withdrawn.

Conclusion

The only stated grounds of rejection has been properly traversed. Applicant therefore respectfully requests that the Examiner reconsider the outstanding rejection and that it should be withdrawn. These arguments do not raise any new issues for consideration. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (202) 371-2589.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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